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Projects and Priorities in Cardiovascular Modeling

MARK A. HLATKY, MD, FACC,* HARRY P. SELKER, MD, MSPH
Durham, North Carolina and Boston, Massachusetts

Studies that either 1) model the likelihood of clinical outcomes as a function of patient characteristics, or 2) examine the factors underlying a specific medical decision are discussed. Although the currently available models represent important contributions, the working group that met during the 1987 Regenstrief Conference identified several important areas for further attention. Described are discussions on ways to improve standardization, accessibility, validation and dissemination of decision models.
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Current Issues in Cardiovascular Modeling

Cardiovascular modeling is a very broad topic, and we have chosen to focus primarily on modeling that supports clinical decision making. Projects such as those in cardiovascular physiology or pharmacokinetics that include modeling but are not aimed at supporting clinical decision making are beyond the scope of this review. We discuss here studies that either 1) model the likelihood of clinical outcomes as a function of patient characteristics, or 2) critically examine the factors underlying a specific medical decision.

Cardiovascular modeling projects may be classified according to the project's clinical focus (Table 1). Most cardiovascular models have concerned manifestations of coronary artery disease, primarily chronic stable angina pectoris and acute myocardial ischemia syndromes (including acute myocardial infarction and unstable angina). There have been some models of syncope and ventricular arrhythmias, but relatively few that examine valvular disease, congenital disease, pericardial disease and other less common cardiac disorders. Examples of these applications and the associated investigators are listed in Table 1.

Another way to classify cardiovascular modeling projects is according to the methodology they employ. The major categories then become 1) clinical prediction rules for diagnosis, triage or prognosis, and 2) decision models that focus on clinical or cost-effectiveness outcomes. The models in Table 1 are cross-classified with use of this schema.

The cardiovascular models cited in Table 1 represent important contributions. Nevertheless, the working group identified a number of important areas that deserve further attention. The following sections describe ways to improve the standardization, accessibility, validation and dissemination of models.

Standardization of Variables in Cardiovascular Models

Several barriers block more widespread use of cardiovascular models (Table 2). One substantial barrier is the lack of standardization in the definition and measurement of key variables in models. Lack of standardization may not only add "noise" to the system, but in some instances may introduce systematic deviations (or bias) in the performance of models. Purely clinical variables have the greatest potential for different definitions among centers. For example, the classification of angina as typical or atypical, stable or unstable, progressive or crescendo, class II or class III or "medically unresponsive" may differ considerably among institutions. Even more "objective" data such as electrocardiographic findings may be interpreted quite differently in different institutions, especially in the absence of standard coding. Variations in either the definition or measurement of such key variables can make transfer of models to another institution difficult.

Greater standardization of nomenclature could facilitate the adoption of cardiovascular models outside the institutions that developed them. Professional associations such as the American College of Cardiology or the American Heart Association could devise and promulgate standards for nomenclature. The role of multicenter trials in standardization can also be considerable because standardization of the definitions of clinical variables across leading centers of cardiovascular investigation is a prerequisite for the conduct

From the *Division of Cardiology, Department of Medicine, Duke University Medical Center, Durham, North Carolina and the †Divisions of General Medicine and Clinical Decision Making, Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts.
Address for reprints: Mark A. Hlatky, MD, Box 31265, Duke University Medical Center, Durham, North Carolina 27710.

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Table 1. Projects and Leading Investigators in Clinical Cardiovascular Modeling

I. Diagnosis
  A. Angina pectoris
    1. George Diamond: CADENZA; Cedars-Sinai Medical Center, Los Angeles, California (1,2)
    2. David Pryor: Duke Cardiovascular Disease Database; Duke University Medical Center, Durham, North Carolina (3)
    3. Robert Detrano: Veterans Administration Medical Center, Long Beach, California and Cleveland Clinic, Cleveland, Ohio (4)
  B. Acute myocardial infarction
    1. Harry Selker, Ralph D'Agostino, Michael Pozen: Tufts-New england Medical Center, Boston, Massachusetts (5)
    2. Lee Goldman: Brigham and Women's Hospital Boston, Massachusetts (6)
    3. Harold Sox: Stanford University, Palo Alto, California (7)
II. Prognosis
  A. Chronic coronary artery disease
    1. Duke Cardiovascular Disease Database (8–11)
    2. Kathryn Davis, Lloyd Fisher: Coronary Artery Surgery Study (CASS) Coordinating Center, Seattle, Washington (12,13)
    3. Katherine Detre: Veterans Administration Cooperative Study and National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty (PTCA) Registry, Pittsburgh, Pennsylvania (14,15)
  B. Acute coronary artery disease
    1. William Knaus: APACHE; George Washington University, Washington, D.C. (16)
    2. Elizabeth Gilpin, Erling Birk Madsden, John Ross, Jr.; University of California, San Diego, California (17,18)
    3. Arthur Moss: Multicenter Postinfarction Research Group, Rochester, New York (19,20)
    4. Robert DeBusk: Stanford University, Palo Alto, California (21)
  C. Valvular disease
    1. Eugene Blackstone: University of Alabama, Birmingham, Alabama, (22)
  D. Arrhythmias and syncope
    1. Wishwa Kapoor: studies of syncope; University of Pittsburgh, Pittsburgh, Pennsylvania (23)
III. Cost-benefit, decision analysis
  A. Milton Weinstein: studies of hypertension and coronary artery bypass surgery; Harvard School of Public Health, Boston, Massachusetts (24–27)
  B. Shan Cretin: University of California, Los Angeles, California (28)
  C. Lee Goldman: Harvard University (29)
  D. Stephen Pauker: studies of coronary surgery and pacemakers; Tufts New England Medical Center, Boston, Massachusetts (30–32)
  E. David Eddy: confidence profile method; Duke University, Durham, North Carolina (33)

of multicenter trials (for example, the Coronary Artery Surgery Study and the Thrombolysis in Myocardial Infarction Trials have been very useful in this regard).

Improving Accessibility of Models

Using standardized key words in publications. The committee noted that a second important barrier to more widespread use of cardiovascular modeling was the difficulty that potential users have in learning about the existence of models and how to use them. One fairly simple method to assist potential users in locating cardiovascular models would be to have all model developers use a uniform set of key words in their published manuscripts. This set of key words would allow bibliographic searching using the *Index Medicus* or computerized Medline searches.

Table 2. Barriers to Adoption of Cardiovascular Models

Nonstandard terminology
Difference in measurement standards
Lack of awareness of models
Lack of model validation
Many models difficult to use

Creating a centralized data base or clearinghouse for models. Another method of improving access to users of models would be to have a centralized data base or clearinghouse for cardiovascular-oriented models. The clearinghouse could contain as little as a brief description of the model and the name of its developer, or could contain as much as the complete specifications of the model and all necessary documentation. Such a clearinghouse could be maintained either by professional societies (such as the American College of Cardiology or the Society for Medical Decision-Making), by independent entities (such as the Regenstrief Institute for Health Care) or by the National Library of Medicine.

The committee felt strongly that the establishment of such a central clearinghouse should be explored. It recommended that the clearinghouse include a basic description of each model and direct interested users to the developer of the model for a complete description of the model and instructions on its use. A clearinghouse that held complete specifications and documentation of models would have a potential advantage because the user would not have to contact the developer of the model. The committee felt, however, that this advantage was more than outweighed by several drawbacks, especially the possibility that the model

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could be used inappropriately or that some of the basic limitations of the model could be misunderstood without communications between the user and the developer. Furthermore, in the case of commercial products, complete divulgence of the contents of the model may be limited for proprietary reasons. Thus, the committee felt that any clearinghouse would be most useful by bringing interested users together with model developers.

Validation and Dissemination of Models

The committee identified several general reasons to recommend that the initial use of a cardiovascular model should involve close communication between the user of the model and its developer or developers. First, any differences in the way the user of a model and its developer measure key variables should be identified and minimized. Second, validation of how a model performs in other institutions is important evidence of its value and, therefore, validation studies should be carefully planned and truly collaborative. Because failure of a model to replicate results in another institution is a major shortcoming, validation studies must be fair and unbiased. Poor replication of a model because of differences in data specification or misunderstanding of how to use the model may halt acceptance of potentially useful clinical tools.

On the other hand, overly hasty acceptance of models is also to be decried. Potential users of clinical prediction rules should understand model limitations and apply proper methodologic standards in evaluation. In particular, validation studies in an independent study population are essential to assess the performance of models. Such studies are particularly useful when performed in other institutions. Additionally, models intended for clinical use should be tested to determine their value over and above clinical judgment and to demonstrate any impact on clinical care. In this way, models intended for clinical use should meet the same type of standards before being accepted as would any other new procedures.

The committee was also concerned about uncritical acceptance of the results of models. These models are meant to supplement and not replace clinical judgment. Marked discrepancies between a model and clinical judgment should be examined closely. In this regard, clinicians should treat models as they would any other consultant. This consideration has an important corollary. To the extent that decision models are used to dictate management of groups of patients, as might be done in setting standards of care or reimbursement policy, model performance must be particularly well validated. This need arises from the lesser opportunity for seasoned clinical judgment to override the model if errors are present. Thus, direct translation of models into policy or payment systems must be particularly cautious.

Table 3. Priority Areas for Modeling

1. Prevention strategies for coronary heart disease
2. Cardiovascular therapies in the elderly
3. Integrated treatment strategies for acute myocardial infarction

Priorities and Recommendations

Clinical questions in need of further modeling. Priorities for future work can be divided into two main areas, namely clinical questions in need of further modeling and methodologic questions that will advance the state of the art. Most clinical modeling arises from clinical dilemmas encountered by physicians in their everyday practice. The committee recognized that most models will continue to be prompted by pressing clinical problems. Beyond the areas that are already topics of cardiovascular modeling (Table 1), there are many additional clinical questions that might benefit from modeling. Potential areas of work include the management of patients with ventricular ectopic rhythm, especially patients with evidence of left ventricular dysfunction; management of patients who have been "ruled out" for myocardial infarction; evaluation of the ambulatory patient with chest pain; evaluation of patients with suspected pulmonary embolism; evaluation of patients with syncope and management of coronary artery disease in patients undergoing vascular surgery procedures. From a clinical perspective, many other areas of interest could clearly be identified to meet the needs of practicing physicians.

In assigning priorities for cardiovascular modeling projects, the committee felt that major consideration should be given to problems that either present major public health hazards or involve allocation of considerable medical care resources, or both. It identified three areas in particular that merit further investigation (Table 3).

The optimal approach to the prevention of coronary artery disease. Considerable uncertainty remains about the best method of prevention, and various strategies need to be evaluated in terms of cost-benefit and cost-effectiveness analyses. In particular, the relative merits of the strategy of population-wide interventions versus the strategy of screening for high risk individuals and initiating individualized therapy need to be assessed. New models should take into account the availability of newer cholesterol-lowering drugs, as well as the new research findings about cholesterol-lowering and the value of aspirin in primary prevention.

Management of cardiovascular disease in the elderly. This will be an increasing problem as the average lifespan lengthens and therapeutic interventions are more often considered in this segment of the population. A major question that could be addressed is the use of expensive technology such as coronary bypass surgery and coronary angioplasty in the elderly population. Clinical cardiovascular modeling could analyze possible age-related changes in the efficacy of such

therapies. In addition, quality of life is often more important than length of life to the elderly patient. Considerable methodologic work needs to be performed to take quality of life into account in the evaluation of clinical management strategies.

The strategy for the treatment of patients with acute myocardial infarction. The advent of the thrombolytic therapy has markedly changed the approach to patients with acute myocardial infarction. Although thrombolytic agents clearly lower the mortality rate, the need for further therapy after thrombolysis (such as angioplasty, bypass surgery and secondary prevention) needs to be addressed. Cost-effective strategies for identifying the high risk patient also need to be evaluated. In view of the relative frequency of acute myocardial infarction and its role of a major cause of premature death, the critical evaluation of various strategies in the care of myocardial infarction should be a major priority.

Other priorities in advancing the field of cardiovascular modeling. These include development of common nomenclature for clinical variables and increased recognition of methodologic standards in performing cardiovascular modeling. Major effort needs to be expended to make models more helpful to the physicians. In particular, models should be made easier to use and easier to understand. The committee felt that considerable work needs to be performed to understand the needs of physicians in decision making in daily practice and improve the interface between models and physicians. Finally, the possible role of regulation of models that provide therapeutic advice to physicians must be addressed.

Conclusions. The committee found that there is a wide variety of ongoing projects in clinical cardiovascular modeling. These projects cover several clinical domains and use several methods. Despite the successes to date, the committee found that models are not well disseminated or frequently used; standard nomenclature and improved communications networks would ameliorate these shortcomings. The committee felt that cardiovascular models should be evaluated as done for other medical technologies, with an initial development phase where they are used in a few institutions, a critical evaluation phase in a wide number of institutions and a phase of widespread dissemination. Work in the future should focus on strengthening the value of models to clinical decision makers and developing models in priority areas such as prevention of coronary disease, cardiovascular care in the elderly and management of acute myocardial infarction.

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